T. Kikalishvili, V. Chumburidze
Emergency Cardiology Center by Acad. G. Chapidze
E-mail: tkikalishvili@yahoo.com, vchumburidze@geosc.ge

WOMEN AND MEN: SEX DIFFERENCES IN CARDIOVASCULAR RISK PREVENTION

Key words: cardiovascular, risk factors, female-specific risk factors, prevention.

FOR REFERENCES. Kikalishvili T., Chumburidze V. Zhenschiny i muzhchiny: razlichiya v profilaktike serdechno-sosudistych zabolevaniy [Women and Men: Sex Differences in Cardiovascular Risk Prevention]. *Neotlozhnaya kardiologiya i kardiovaskulyarnye riski* [Emergency cardiology and cardiovascular risks], 2018, vol. 2, no. 1, pp. 258–269.

Cardiovascular disease (CVD) is the leading cause of death in women, and knowledge of the clinical consequences of atherosclerosis and CVD in women has grown tremendously over the past 20 years. Research efforts have increased and many reports on various aspects of ischaemic heart disease (IHD) in women have been published highlighting sex differences in pathophysiology, presentation, and treatment of IHD. For the past three decades, dramatic declines in heart disease mortality for both men and women have been observed, especially in the > 65 years' age group. But despite it according to the Global Burden of Disease, in 2004, CVD caused almost 32 % of deaths in women worldwide vs. 27 % in men. In Europe, 54 % of all females' death are from CVD vs. 43 % in men. Recent evidence has emerged that recognizes new, potentially independent, CVD risk factors exclusive to women. In particular, common disorders of pregnancy, such as gestational hypertension and diabetes, as well as frequently occurring endocrine disorders in women of reproductive age are associated with accelerated development of CVD and impaired CVD-free survival. With the recent availability of prospective studies comprising men and women, the equivalency of major risk factors prevalence and effects on CVD between men and women can be examined. Furthermore, female-specific risk factors might be identified enabling early detection of apparently healthy women with a high lifetime risk of CVD. Therefore, we examined the available literature regarding the prevalence and effects of the traditional major risk factors for CVD in men and women.

Almost 62 million Americans have one or more types of cardiovascular disease and, of these, more than 32 million are female. This translates into an average of 1 in 5 women, making cardiovascular disease the leading killer of women in the U.S., responsible for more than half a million deaths a year [1]. While it has been known for some time that differences exist between the sexes regarding coronary heart disease, it has only been in the last 10 years that these disparities in incidence, morbidity, mortality, risk factors, diagnosis, and treatment have been explored. Research has shown a gap in the utilization of medical therapy, diagnostic studies, and revascularization procedures involving women. In addition, women's outcomes after myocardial infarction have been consis-tently demonstrated to be poorer than those of men. Another important issue that has just started to be addressed is that the predominantly male-focused cardiovascular research has been generalized to women. Only in recent years have women been included in clinical trials or databases in sufficient numbers for sex-based analysis of the data [2]. The topic of cardiovascular disease in women is diverse and complex. In this article, some of the important issues will be introduced and discussed, highlight the current understanding of the problem and to emphasize the areas in which further study and progress is needed.

Cardiovascular disease (CVD) remains the leading cause of death in women and, according to the most recently released United States statistics, accounted for 398 086 female deaths in 2013 [1]. After the year 2000, both the death rates and the number of cardiovascular deaths have shown a similar, if not steeper, downward trend in American women compared with men. However, when looking at different age groups, the decrease in mortality appears to have slowed down since 2000 in middle-aged women and men (age 35–54 years), whereas it has continued steadily among older people. In addition to an overall decline in cardiovascular mortality from population statistics, there has been a decline in hospital mortality rates for acute myocardial infarction (AMI) among American women and men of all ages, which has been more substantial in women than in men.

It should be noted that these favorable trends are not universal. For example, they do not apply to Eastern Europe, where mortality from both IHD and CVD is still rising for both women and men. Exceptions are Hun-gary, whose rates levelled off (at very high rates) in the mid-1990s, and Poland and the Czech Republic, whose rates have tended to decline since the mid-1990s [3]. In the Russian Federation, mortality rates from IHD and CVD for both women and men during 1995–1998 were among the highest in the world. The data for Georgia are also very impressive.

Recent data suggest stagnation in the improvements in incidence and mortality of coronary heart disease, specifically among younger women (< 55 years) [2]. It is imperative that we understand the mechanisms that contribute to worsening risk factor profiles in young women to reduce future atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality. Increased recognition of the prevalence of traditional ASCVD risk factors, and their differential impact in women, as well as emerging, nontraditional risk factors unique to or more common in women, contribute to new understan-ding of mechanisms leading to these worsening out-comes for women (Figure 1).

Traditional risk factors in women: diabetes, smoking, obesity and overweight, physical inactivity, dyslipidemia

More than 13.4 million US women have a diagnosis of DM, and 90 % to 95 % of these women have type 2 DM (T2DM). The rate of T2DM in Hispanic women is more than double when compared with non-Hispanic white women (12.7 % versus 6.45 %, respectively) [3]. The increasing prevalence of T2DM is concerning because it is a potent risk factor for ASCVD and has long been recognized to confer greater risk for ASCVD death in women compared with men. In a meta-analysis of over 850 000 individuals, the relative risk for CVD was 44 % greater in women with DM than in similarly affected men. The presence of DM thus represents an imperative for aggressive CVD prevention strategies in women. Growing evidence suggests that diabetic women have more adverse ASCVD risk factor status than diabetic men, consisting of impaired endothelium-dependent vasodi-lation, a hypercoagulable state, worse atherogenic dyslipidemia, and more metabolic syndrome.

Although there are fewer adult (≥ 18 years) women smokers (15 % versus 19 % of men), a recent meta-analysis reported that in all age groups, with the exception of the youngest (30–44 years), women had a 25 % increased risk for CAD conferred by cigarette smoking compared with men. The combination of smoking with oral contra-ceptive use has a synergistic effect on risk of acute myocardial infarction (MI), stroke, and venous throm-boembolism [4].

The impact of obesity on the development of CAD seems to be greater in women than in men. In the Framin-gham Heart Study, obesity increased the relative risk of CAD by 64 % in women, as opposed to 46 % in men [5]. Weight gain during adult years is highly related to deve-loping a greater ASCVD risk factor burden, and this has been observed with relatively modest weight gain in pros-pective studies, such as the Framingham Offspring Study.

Dyslipidemia has the highest population-adjusted risk among women, at 47.1 %, compared with all other known risk factors for ASCVD. However, this greater ASCVD risk is typically not observed before menopause, even if cholesterol levels are elevated. Lifestyle modifi-cations, including diet and exercise, are of critical importance in the primary and secondary prevention of ASCVD. Pharma-cological therapy of hyperlipidemia for secondary pre-vention has clearly been shown to be equally effective in women and men for reduction of recurrent cardiac events and ASCVD mortality.

Recent data from the Center for Disease Control and Prevention indicated that between 2005 and 2012, only 45 % of 78.1 million adults eligible for cholesterol-lowering medications actually took them. Of even more concern though is that recent reports have identified sex-specific differences in both treatment and adherence

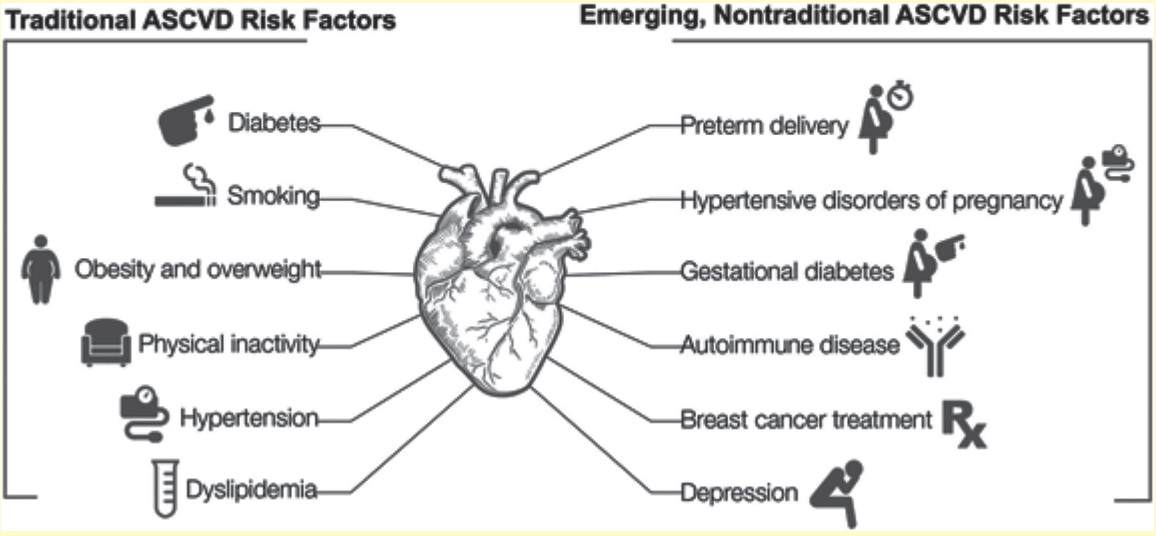

Figure 1. Traditional and nontraditional atherosclerotic cardiovascular disease (ASCVD) risk factors in women.

to lipid-lowering medications; women are less likely to be prescribed statin therapy, and compliance is variable. Reasons for this disparity are unclear at the present time, but underscore the need for additional physician and patient awareness of the benefits of lipid-lowering therapy in women [6].

Nontraditional risk factors in women: pregnancy related disorders, gestational diabetes mellitus, autoimmune diseases- Rheumatoid Arthritis and Systemic Lupus Erythematosus, radiation and chemotherapy, depression, menopause.

Preterm delivery (PTD) defined as birth at < 37 weeks' gestation complicates 5 % to 12.7 % of deliveries worldwide. The underlying causes and mechanisms of PTD delivery are not yet completely understood. The main mechanisms that have been suggested are inflammation, infection, and vascular diseases. A recent study concluded that PTD is an independent risk factor for subsequent long-term cardiovascular morbidity and cardiovascular-related hospitalizations. The risk for ASCVD was further increased with a history of early PTD (< 34 weeks' gestation). Earlier occurrence of preeclampsia in pregnancy is associated with poorer outcomes; in addition, the severity of preeclampsia is correlated with the severity of CVD later in life [7].

Ongoing epidemic of obesity and DM has led to more T2DM in women of childbearing age, resulting in an increase in the number of women with undiagnosed T2DM at pregnancy, and thus, women found to have DM in the first trimester are classified as having T2DM. Gestational DM is defined as newly diagnosed DM beyond the first trimester of pregnancy [8]. Gestational DM increases the risk of developing T2DM by 7-fold, which is a major risk factor for subsequent ASCVD, but also raises CVD risk (2-fold for stroke and 4-fold for MI) independently of the overt development of T2DM.

For most systemic autoimmune disorders, there is a clear sex difference in prevalence, making this a more common ASCVD risk factor in women. The microvasculature in women may play an important role in the predisposition of women with autoimmune diseases to develop accelerated CVD. The female to male ratio for rheumatoid arthritis is 2.5:1 and for systemic lupus erythematosus is 9:1. Patients with rheumatoid arthritis have a 2- to 3-fold higher risk of MI and a 50 % higher risk of stroke. For systemic lupus erythematosus, recent case-control series has indicated that the risk of MI is increased between 9- and 50-fold over that in the general population [9].

Women with pre-existing cardiac risk factors have greater absolute increases in risk from radiotherapy. In a recent population-based case-control study, women irradiated for cancer of the left breast had higher rates of CAD events than women receiving radiation to the right breast. Moreover, the rate of CAD events increased by 7.4 % per gray of the mean radiation dose delivered. Radiation-induced heart disease can also manifest as valvular and cardiomyopathic processes. Patients with breast cancer who have undergone anthracycline-based therapy and patients who have had mediastinal radiation therapy are candidates for long-term cardiac surveillance programs. An expert consensus statement from the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommends evaluation based on signs and symptoms and echocardiographic surveillance continuing 5 years after treatment in high-risk patients and 10 years in all other patients [10].

Limited evidence suggests that depression and other psychosocial risk factors might be more powerful risk factors in younger individuals, and especially in young women. Although few women develop CVD at a young age, the lifetime risk in women at age 50 years is ≈ 40 %, and therefore, identification of risk factors in young populations may provide long-term benefit by facilitating early prevention. Furthermore, young women have been underrepresented in studies of CVD, have higher rates of depression, and have higher mortality rates after acute MI compared with men. Unfortunately, psychological interventions aimed at reducing stress or treating depression or other psychosocial risk factors have shown little to no effect on IHD incidence and total or cardiac mortality, although they do achieve small reductions in anxiety and depression in patients with IHD. When results are reported separately by sex, men show a borderline statistically significant benefit [OR 0.73, 95 % confidence interval (CI) 0.51–1.05], whereas in women, the estimate is null (OR 1.01, 95 % CI 0.46–2.23). It may be that traditional psychosocial interventions do not work well for women and that strategies that address more specifically women's needs and stressors should be developed.

Premenopausal women are relatively protected against CVD, compared with age-matched men. However, this sex gap narrows after menopause. This long-standing observation led to a hypothesis that ovarian steroid hormones and, in particular, estrogens, were cardio protective, initially supported by retrospective observational studies. However, such conclusions were refuted by randomized clinical trials of both primary and secondary prevention of ASCVD. The discordance was surprising in light of the beneficial physiological effects of estrogen on the vascular endothelium at the cellular and molecular levels, on blood vessels in animal CVD models, and on lipids and insulin-resistance biomarkers; as such, menopausal hormone therapy (MHT) became one of the most controversial areas in women's health. The results of the major randomized clinical trials, the Women's Health Initiative (WHI) and the Heart Estrogen/Progestin Replacement Study (HERS), led to dramatic changes in clinical practice in the mid-2000s, with marked declines in the use of MHT worldwide [10].

Primary prevention of Cardiovascular disease in Women: focus on prevention guidelines.

For the first time in 2007, the AHA published evidence-based guidelines focused on the primary prevention of CVD in women, which were subsequently updated in 2011 as effectiveness-based guidelines. Early screening and a complete CVD risk assessment were advised to reduce the pervasiveness of CVD in women who were previously largely excluded or minimally represented in cardiovascular research. The transformation from evidence-

based to effectiveness-based guidelines denoted a shift from pure clinical research as the basis of recommendations to an approach that encompasses benefits and risks observed in clinical practice. The Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries (INTERHEART) study identified 9 easily measured risk factors (smoking, lipids, hypertension, DM, obesity, diet, physical activity, alcohol consumption, and psycho-social factors) that account for over 90 % of the risk for acute MI. Importantly, the magnitude of the ASCVD risks for men and women were similar, but the impact of modifying the risks was greater in women. Thus, large studies have demonstrated that lifestyle intervention for primary prevention can decrease the incidence of ASCVD as well as the associated mortality rates in both women and men.

Data on aspirin for primary prevention of CVD in women have been more limited. In the large-scale Women's Health Study (WHS), almost 40 000 healthy women over the age of 45 years were randomly assigned to low dose ASA (100 mg every other day) or to placebo for 10 years, and major CVD events were evaluated. Overall, the trial showed a statistically non-significant 9 % reduction in the primary composite outcome of major CVD events with low-dose ASA. ASA significantly lowered the risk of total stroke by 17 % (CI, 0.01–0.31) and the risk of ischemic stroke by 24 % (CI, 0.07–0.37) in women, but did not lower the risk of MI or cardiovascular death. This contrasts to the significant reduction in MI and neutral effect on stroke for primary prevention in men observed in the Physicians' Health Study. Moreover, as in men, ASA increased gastrointestinal bleeding risks and the risk of hemorrhagic stroke. However, in subgroup analyses, the CVD risk/benefit ratio appeared to be directly linked to a woman's age; in WHS participants over age 65 years, ASA was clearly associated with evidence of benefit for both ischemic stroke and MI. The AHA effectiveness-based guideline recommendations for the prevention of CVD in women were thus derived to state that for primary prevention, ASA therapy (81 mg daily or 100 mg every other day) can be useful in women ≥ 65 years of age if BP is controlled, and benefit for stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorr-hagic stroke (Class IIa, Level of Evidence B) and may be reasonable for women < 65 years of age for ischemic stroke prevention (Class IIb, Level of Evidence B). It is important for physicians to be aware that, despite the increased risk for ASCVD in female patients with DM, having DM alone does not qualify them for ASA therapy. Physicians must still perform a proper ASCVD and bleeding risk assessment before making recommenda-tions.

The effectiveness of statins in primary prevention in women is still controversial. A recent meta-analysis of 27 trials of statin therapy concluded that the proportional reduction in major vascular events per 1.0 mmol/L reduction in LDL cholesterol was similar for men and women (risk ratio for women 0.84 [99 % CI 0.78–0.91]; risk ratio for men 0.78 [99 % CI 0.75–0.81]), irrespective of the baseline level of ASCVD risk or subtype of ASCVD outcome assessed. Although the results were slightly more favorable for men than for women (P for heterogeneity by sex < 0.05), the guidelines for statin use are the same for both sexes (Figure 2). A recent meta-analysis, including 13 statin trials with 91 140 participants, found that statin therapy was associated with a 9 % increased risk of developing incident DM, odds ratio 1.09 (95 % CI, 1.02–1.17); however, no sex-specific ana-lysis was performed [11]. Overall, the benefit of statins from reduction in coronary events seems to exceed the risk related to DM in both men and women.

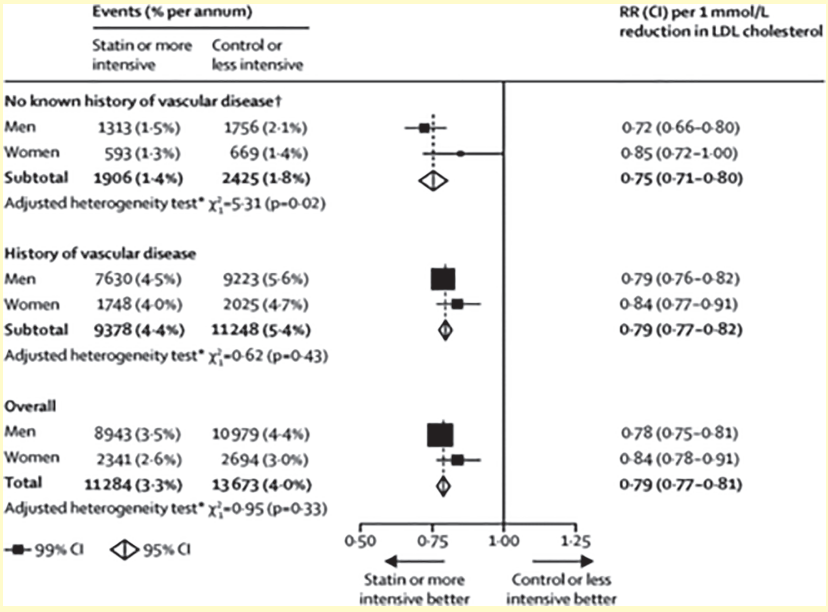

Figure 2. Effects on major vascular events per 1.0 mmol/L reduction in low-density lipoprotein (LDL) cholesterol, subdivided by history of vascular disease and sex.

Clinical manifestations of CVD also differ between sexes, thus making diagnosis challenging. Symptoms frequently experienced by men, such as oppressive or constrictive chest pain and dyspnea have been traditionally recognized as typical of myocardial ischemia, in light of the strict correspondence with obstructive coronary artery disease. Conversely, women more often suffer from abdominal pain, dizziness, shortness of breath, frequent indigestion, unusual fatigue: in such cases, the absence of severe coronary artery disease has caused an important misperception, so that the term «atypical» symptoms has been commonly used as synonymous of «low probability of myocardial ischemia». Moreover, the evidence that both epicardial coronary artery disease and microvascular dysfunction in women may potentially manifest the same symptoms has greatly contributed to generate confusion. As consequence, the prognostic value of chest pain in women has been greatly underestimated. This derives partly by the evidence that women in the Framingham study developed chest pain more often than men, but it rarely progressed to myocardial infarction. The predictive value of angina increased only among older subsets of women. According to the most recent literature data, we think that such important issue has to be focused by another point-of-view: irrespectively of the precise pathophysiological mechanisms, men and women may equally suffer from myocardial ischemia and are worthy to be properly treated. The acknowledge of gender differences by physicians is crucial for ensuring the most appropriate treatment strategy in both sexes [12].

Table 4 lists recommendations for the design, conduct, and reporting of future CVD trials in women. A 2011 report from the Institute of Medicine Committee on Women's Health Research recommended that the government ensure adequate participation of women in trials and analyses and reporting of data, both efficacy and adverse effects, by sex [1]. The availability of such data will inform future guidelines and facilitate the translation of research findings into practice. It will be important to determine to what extent these data and their dissemination can reduce gender disparities in preventive care and improve clinical CVD outcomes for women.

Table 4. Recommendations for Future Cardiovascular Trials in Women

Include equal representation of women and men unless adequately justified
Limit exclusion criteria and remove upper age limit to improve the generalizability of results and the projection of effectiveness in clinical practice
Women – only trials should be limited to the study of conditions unique to or predominate in women
Cardiovascular end points should include the scope of outcomes significant for women, including all acute coronary syndromes, fatal coronary heart disease, stroke (thromboembolic and hemorrhagic), and heart failure
Quality-of-life measures should be part of outcomes evaluated by gender
Gender-specific analyses should be conducted and published for both efficacy and safety
Reasons for no adherence to interventions should be documented according to gender
Cost-effectiveness analysis should be conducted and gender-specific data published
Gender-specific power calculations should be conducted and published
Dissemination of results should include communication regarding any significant gender differences in efficacy and adverse effects

Conclusion

It was found out that the effects of elevated blood pressure, overweight and obesity, and elevated cholesterol on CVD outcomes are largely similar between women and men, however prolonged smoking is significantly more hazardous for women than for men. With respect to female-specific risk factors only associations (and no absolute risk data) could be found between preeclampsia, gestational diabetes and menopause onset with the occurrence of CVD. This review shows that CVD is the main cause of death in men and women, however the prevalence is higher in women. Determination of the CV risk profile should take into account that there are differences in impact of major CV risk factors leading to a worse outcome in women. Lifestyle interventions and awareness in women needs more consideration. Furthermore, there is accumulating evidence that female-specific risk factors are of influence on the impact of major risk factors and on the onset of CVD. Attention for female specific risk factors may enable early detection and intervention in apparently healthy women. Studies are needed on how to implement the added risk factors in current risk assessment and management strategies to maximize benefit and cost-effectiveness specific in women. Differences in epidemiology may reflect important aspects of cardiovascular pathophysiology that differ between the sexes. Eventually, a better understanding of these processes may improve the clinical management of IHD in women, because it may help to devise new strategies for the prevention, detection, and treatment of IHD that are better tailored to women [13].

References:

[1] Mozaffarian D., Benjamin E.J., Go A.S., et al., American Heart Association Statistics Committee and Stroke Statistics Subcommittee Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation*. 2015;131: e29–322.

[2] Wilmot K.A., O'Flaherty M., Capewell S., Ford E.S., Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. *Circulation*. 2015;132:997–1002.

[3] Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. *Department of Health and Human Services*; 2014.

[4] Pomp E.R., Rosendaal F.R., Doggen C.J. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. *Am J. Hematol*. 2008.

[5] Wilson P.W., D'Agostino R.B., Sullivan L., Parise H., Kannel W.B. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002; 162: 1867–1872.

[6] Safford M.M., Gamboa C.M., Durant R.W., Brown T.M., Glasser S.P., Shikany J.M., Zweifler R.M., Howard G., Muntner P. Race-sex differences in the management of hyperlipidemia: the REasons for Geographic and Racial Differences in Stroke study. *Am J. Prev Med*. 2015; 48: 520–527.

[7] Linnй Y., Dye L., Barkeling B., Rцssner S. Long-term weight development in women: a 15-year follow-up of the effects of pregnancy. *Obes Res.* 2004; 12: 1166–1178.

[8] del Rincyn I., Polak J.F., O'Leary D.H., Battafarano D.F., Erikson J.M., Restrepo J.F., Molina E., Escalante A. Systemic inflammation and cardiovascular risk factors predict rapid progression of atherosclerosis in rheumatoid arthritis. *Ann Rheum Dis*.

[9] Peters M.J., Symmons D.P., McCarey D. et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010; 69: 325–331

[10] Mariana Garcia, Sharon L. Mulvagh, C. Noel Bairey Merz, Julie E. Buring, JoAnn E. Manson. Cardiovascular Disease in Women. *Clinical Perspectives. Circulation Research.* 2016; 118: 1273–1293.

[11] Brewer L.C., Svatikova A., Mulvagh S.L. The Challenges of Prevention, Diagnosis and Treatment of Ischemic Heart Disease in Women. *Cardiovasc Drugs Ther*. 2015; 29: 355–368.

[12] Leonarda Galiuto, Gender differences in cardiovascular disease. DOI10. 15761 /JIC. 1000107.

[13] Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors?: Position Paper from the Working Group on Coronary Pathophysiology and Microcirculation of the European Society of Cardiology. *Cardiovascular Research*, Volume 90, Issue 1, 1 April 2011, Pages 9–17.

[14] Adler N.E., Adashi E.Y., Aguilar-Gaxiola S. et al. , Institute of Medicine's (IOM) Committee on Women's Health Research. *Women's Health Research: Progress, Pitfalls, and Promise*. Washington DC: National Academies Press; 2010.

Поступила 18.03.2018